Regulatory challenges in developing new treatments for neglected infectious diseases

Author
Bob Clay, Highbury Regulatory Science/Kinapse Consultant/Managing Director at Highbury Regulatory Science and Chief Regulatory Officer at Kinapse Ltd, UK.

Keywords
Article 58; WHO Prequalification of Medicines Programme (PQP); Prequalification; Neglected tropical diseases; Malaria; AIDS; HIV; Tuberculosis; Target product profile (TPP); Product development; Stringent regulatory authorities (SRAs).

Abstract
Developing new treatments for neglected tropical diseases requires multi-stakeholder collaboration to identify target product profiles (TPPs) both for treatment and diagnostic strategies. Many national medicines regulators in the endemic regions do not have the capacity to undertake full reviews of novel medicines, so the development of stringent regulatory procedures by the WHO, the US FDA and the European Medicines Agency (EMA) provides an important step in supporting access. Nevertheless, this complex process needs improvement both through better understanding of procedures such as Article 58 and more proactive partnership approaches represented by WHO Collaborative Registration Procedures.

Introduction
In 2016, as a follow-up to the “Millennium Goals”, the United Nations launched its wide-ranging and ambitious “Sustainable Development Goals”. One of the included targets is: “By 2030, to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases”. New medicines are needed to make a contribution to this agenda, but without access to these new treatments and diagnostic technologies the targets are unlikely to be met.

In many of these epidemic diseases, development should be focused on the most vulnerable populations, often children and pregnant women; however, even in the developed markets these groups often have more limited treatment options. Some diseases have a strong association with poverty (eg, tuberculosis) and the absence of immediate economic support both initial registration and post-marketing surveillance. This may be addressed through building capacity and engaging stringent regulatory authorities (SRAs) that have introduced mechanisms to undertake assessment of medicinal products not intended for their own markets, eg, Article 58 in the EU.

The regulatory challenges are common to all areas of drug development, but have an additional degree of complexity in the setting of tropical (neglected) infectious diseases. These include: development of novel drug combinations; early studies in children and pregnant women; managing clinical trials in the endemic setting; and concomitant diseases or malnutrition. This article selects examples which illustrate approaches to developing a regulatory strategy.

The diseases
The Bill & Melinda Gates Foundation highlight a range of diseases that fall within the scope of this discussion: enteric and diarrhoeal diseases; HIV; malaria; neglected tropical diseases; pneumonia; tuberculosis. Fortunately, as a result of global efforts many of these diseases are in decline; however, the social and economic cost remains enormous. Malnutrition, pneumonia and diarrhoeal diseases are major causes of childhood mortality. Malaria alone results in the death of 500,000 people every year, mainly in sub-Saharan Africa. The path to elimination of these diseases is multifactorial and new medicines and diagnostics are a key part of the solution. The success in reduction of malaria-related deaths (48% between 2000 and 2014), is primarily due to distribution of insecticide-treated bed nets, the wider introduction of artemisinin-based combination therapies (ACT) and access to rapid diagnostic tests.

However, the limited availability of suitable diagnostics results in inappropriate use and development of resistance. Malaria is only one of many possible causes of fever in children, and diagnosis by microscopic examination of blood films is a skilled process with limited availability in the endemic areas – patients may be a long distance from suitable laboratory facilities. Alternative approaches, including antigen testing or molecular (polymerase chain reaction (PCR)) rapid tests, may not be widely available or too costly. Similarly, the challenge presented by multidrug-resistant tuberculosis would be reduced markedly by the introduction of rapid diagnostics that would identify drug resistant organisms at the point of care.

The range of infectious organisms is diverse, including viral, bacterial and parasitic diseases. In parasitic diseases such as malaria there is a complex parasite lifecycle in the host and this allows many points for potential intervention in the disease, but also multiple opportunities for development of resistance. It may be relatively easy to ensure infants are protected under bed nets in homes that are sprayed with insecticide, but protecting older children is more challenging. Additionally, the mosquito may change its feeding times in response to the measures taken by the local community. Malaria also demonstrates a geographic diversity with five different parasite species responsible for infection: Plasmodium falciparum is responsible for the majority of deaths and the most prevalent species in sub-Saharan Africa; Plasmodium vivax is the most prevalent species in Southeast Asia and Latin America. In the Sahel, the occurrence of malaria is highly seasonal and associated with wetter periods, with most malaria infections occurring in a three- to four-month period of the year.
Target product profiles

A key element of any regulatory strategy is the target product profile (TPP) which provides a summary of the development goals and line of sight to the needs of the patient while charting the key requirements to achieve regulatory approval. It is important to seek stakeholder input and capture the debate, so that the development pathway is well documented. One approach based on draft FDA Guidance9 follows a US labelling format, and is useful in providing a structured approach to the product characteristics and annotation with the relevant supporting evidence.

Several PDPs utilise a TPP approach to guide their development plans and ensure their partners are focused on the critical factors. Burrows et al9 describe TPPs for elimination/eradication of malaria for treatment and prevention: single exposure radical cure and prophylaxis (SERCaP) and single exposure chemoprotection (SEC) (see Figure 1). For a variety of reasons, notably prevention of resistance, combinations are being developed for the treatment of malaria, and therefore, target candidate profiles (TCPs) are employed. In addition to safety, efficacy and potential for resistance, they highlight the importance of affordability which would influence manufacturing and formulation choices during development.

Chatelain and Ioset8 describe the importance of developing TPPs in neglected tropical diseases and present an example in visceral leishmaniosis (VL) for developing combinations of existing agents with new drugs. They highlight the importance of a short course of treatment (up to ten days); treatment cost; stability in tropical conditions; and the need to treat immunocompromised patients, among the features of potential new treatments.

Koel et al describe a TPP for new TB drugs, highlighting the importance of a number of key attributes including; activity against resistant isolates; strong bactericidal activity effectiveness against dormant forms; shortened duration of treatment (four to six months); lower dosing frequency and pill burden; as well as reduced drug interaction potential. This TPP addresses a very different set of challenges to that presented for malaria. Tuberculosis is treated for long durations, up to two years in multi-drug resistant cases, regimens contain multiple drugs and recurrence/re-infection rates are high. A greater focus on target regimens and diagnostics is important. This was highlighted by the “Critical Path to TB Regimens” (CPTR)10 which was established as a public-private partnership to facilitate the advance of promising combinations. The increasing challenge of drug-resistant forms of TB (usually described as multi-drug resistant (MDR-TB), extensively-drug resistant (XDR-TB) or totally drug-resistant (TDR-TB)) highlights the importance of diagnostic testing. Using treatment regimens that include agents for which resistance is already observed will increase the likelihood of resistance development of other components. Following a 2014 consensus meeting, the WHO11 published a set of TPPs in relation to diagnostic tests: rapid, biomarker-based non-sputum based test for detecting TB; a community-based triage or referral test to identify people suspected of having TB; rapid sputum-based test for detecting TB at the microscopy centre level of the healthcare system; and next-generation drug susceptibility test to be implemented at peripheral levels of the healthcare system to inform decisions about first-line treatment regimens.

These TPPs are more detailed than those that have been developed for disease treatments, reflecting the different approaches and needs of the diagnostic industry. It is worth noting that many of these approaches are also critical in the development of new drugs and would be applicable to clinical trials.

The role of regulatory authorities

Cooperation between medicines regulatory authorities (MRAs) is represented by bilateral agreements, regional collaborations, and international standards organisations. The majority of MRAs do not have the capacity to evaluate new medicines and are dependent to various degrees on the assessments undertaken by SRAs, ie, members of the International Conference on Harmonisation (ICH), an ICH Observer (Swissmedic, Health Canada, WHO) or a country associated with an ICH member through a mutual recognition agreement (eg, Australia). In diseases common to all regions, the innovator will normally obtain approval in SRAs and subsequent approvals in other countries would

![Figure 1: Breakdown of the ideal medicine into different candidate profiles.](image-url)
follow, based on regulatory requirements and commercial demand. In the case of generic medicines, diagnostics and vaccines the WHO prequalification procedure (POP) offers an opportunity for manufacturers to have their dossiers and manufacturing facilities reviewed to provide assurance of quality, safety and efficacy of their product. The POP is intended for use across a number of high-burden diseases (e.g., HIV, malaria, TB and reproductive health) where the medicine appears in WHO essential medicines lists or treatment guidelines.

It might be assumed that SRAs have limited interest in the development of medicines for use outside their jurisdiction, but this is not the case; both the FDA and EMA have policies supportive of such activities. However, there are many challenges presented in applying regulatory science and standards well-established for the review of medicines in Europe and the US that may not be appropriate or feasible in the endemic countries. The review teams may be less familiar with the diseases or the conditions in the endemic regions, which may result in sub-optimal decisions. This may be addressed through workshops hosted by regulators to facilitate stakeholder interactions, such as one held recently by the FDA on malaria that considered the use of modelling to address dose selection, combination drug development and suitable methods for endpoint measurement in clinical trials.

Prior to the introduction of Article 58 of Regulation (EC) No 726/2004, there was no clear mechanism for the review and approval of medicines for diseases that had been long eradicated in Europe (e.g., trachoma) or observed in a different setting (e.g., prevention of malaria in travellers versus treatment of acute malaria in endemic areas). The Article 58 procedure is the same as the centralised procedure, concluding with the issue of a CHMP opinion, but there is involvement of the WHO during the assessment. It has a broad scope and is framed to allow the review of “medicinal products” not intended to be marketed in the EU. It has been used to support alternative versions of HIV products to prevent re-importation from LMIC markets, or to address the “sunset clause” that would apply to medicines approved but not marketed. Due to limited participation, only seven opinions were granted up to 2015 and, following concerns regarding the effectiveness of the procedure in achieving improved access in LMICs, a strategic review was commissioned by EMA, the European Commission and the Bill & Melinda Gates Foundation in 2015. This review identified five major barriers to the use of Article 58 achieving its full potential: manufacturers unclear/unconvinced of the benefits; prohibitive or burdensome fees; MRAs unprepared to approve these new drugs as a result of the restricted approval conditions. Therefore, inclusion in WHO treatment guidelines may be required prior to approval in the endemic countries.

The EU paediatric requirement for marketing authorisation needs to be considered; for malaria, it must be hoped that the sponsor would intend to develop the product for children and that the opportunity to seek protocol assistance would not represent any disadvantage. Article 58 procedures encourage early engagement with the WHO and MRAs to facilitate future development and positioning in treatment guidelines.

In 2013, the WHO launched a collaborative registration procedure (CRP) following a pilot phase in which manufacturers and MRAs agreed to utilise the prequalification dossier and WHO assessments to streamline national approvals. This scheme excludes prequalification based on SRA review and the WHO recently launched a pilot scheme to address this gap. This pilot scheme could expand the usage due to a broader definition “public health needs” rather than the limited categories associated with POP. The CRP allows the submission of common technical document (CTD) format to the national MRA, and sharing of the SRA/WHO-POP assessment and inspection reports with the aim of an accelerated decision, a 90-day registration procedure by the MRA. One concern that remains regarding the CRP is the participation of MRAs, primarily in Africa, but this should evolve with increased confidence in the procedure. The list of potential MRAs includes several other agencies, e.g., Canada, Switzerland and Australia, and the developer should explore some of these other agencies, particularly where bilateral agreements already exist. Australia may be a suitable option for many countries in South-east Asia and the potential for collaborative reviews should be considered.

Conclusion
Within this article, our focus has been on understanding the product and development needs and developing TPPs and the complexity of registration strategies. The delivery of new medicines and diagnostics to patients is a key element of the global health agenda and makes use of every skill and area of knowledge in the regulatory scientist’s toolbox. The most important element is teamwork across every discipline and function engaged in the development and delivery of health improvement.

References


